Value of Sequels

Is It Safe to Include Nitrous Oxide in Your Anesthetic?

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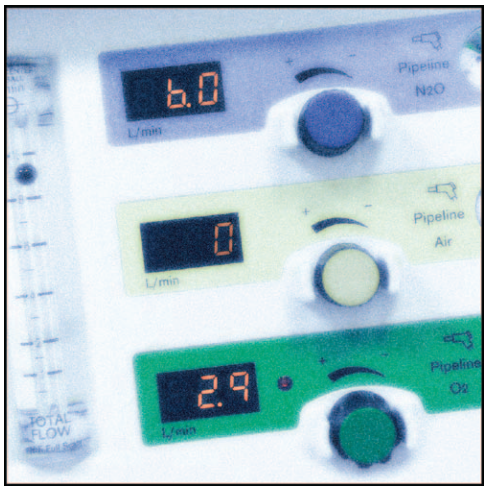
THE optimal choice of anesthetic agent for the patient with cardiovascular disease undergoing noncardiac surgery has been a topic of interest for decades. On the basis of animal models, cohort studies, or small trials, experts had advocated high-dose narcotic techniques while expressing concern about the theoretical potential of developing isoflurane-induced coronary steal.[1,2] Fortunately, we have moved into the era of large-scale clinical trials that have allowed us to determine the evidence basis for the optimal agent in such patients. In this issue of ANESTHESIOLOGY, Leslie *et al.*[3] report on the long-term results of their investigation into the potential harmful effects of nitrous oxide and demonstrate no effect compared with placebo.

In the context of the movies, sequels rarely live up to the hype of the original; however, this is not the case for clinical trials. In the original Elimination of Nitrous Oxide in the Gas Mixture for Anesthesia (ENIGMA) trial investigating the effect of nitrous oxide on outcome,[4] cardiovascular morbidity was significantly higher on long-term follow-up.[5] This incidental and provocative finding was in contrast to the primary outcome of no difference in length of stay compared with placebo and therefore should be considered hypothesis generating.[4] This led the authors who designed the ENIGMA-II trial to investigate both the short- and long-term effects of nitrous oxide compared with placebo in a group of high-risk cardiovascular patients. This sequel to the original trial included a much larger sample size to address this new hypothesis and redesign of the protocol to ensure that both groups utilize the same oxygen concentration. They found no difference in the primary outcome of death and cardiovascular events in either the short-term or on long-term follow-up.[3,6] It has become increasingly clear that actions in the perioperative period may have long-term implications, and including a long-term follow-up is increasingly important.[7] Therefore, the assessment of long-term follow-up of the ENIGMA-II trial participants was critical in ensuring that the question of nitrous oxide's safety was fully addressed.



"... we can conclude that nitrous oxide is safe for the general population and in patients with cardiovascular disease undergoing noncardiac surgery when the concentration of oxygen is held constant."

The undertaking of such large-scale clinical trials is very complex, and the trial leaders should be commended for completing such a Herculean task. The authors do point out some of the limitations of their analysis given the size of the task. In particular, not all of the sites could perform the complete long-term follow-up, and even for those who could, there was a group of patients who were lost to follow-up. The authors attempted to address these issues through sophisticated statistical approaches that help ensure robustness of their conclusions. Another key issue in any such design is that the assessment of the long-term outcome includes medical record review and patient interviews. The absence of a formal screening protocol for out-of-hospital events can introduce bias given the variability in symptoms and diagnosis, but such bias will likely affect both groups similarly in such a large trial. The change in the oxygen concentration

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between ENIGMA and ENIGMA-II may also suggest that the original finding was not spurious but a function of the oxygen concentration. This does not negate the current findings but does suggest that more research is needed to determine whether the original protocol for general anesthesia is truly associated with worse long-term outcomes. Finally, investigators have included among their outcomes the assessment of long-term disability. This investigative group is leading the field in the assessment of disability as an important outcome to patients. They note in their article that they are currently using the World Health Organization Disability Assessment Schedule instrument.[8] Importantly, they were unable to show any difference in a disability outcome between nitrous oxide and placebo.

In summary, the investigators should be congratulated for following up on their provocative finding of long-term cardiovascular complications associated with nitrous oxide use with a large-scale sequel trial directed at addressing this question assessing both short- and long-term outcomes. On the basis of the results, we can conclude that nitrous oxide is safe for the general population and in patients with cardiovascular disease undergoing noncardiac surgery when the concentration of oxygen is held constant. ENIGMA and ENIGMA-II have demonstrated the importance of assessing short- and long-term outcomes and of following up novel associations with definitive trials in which hypothesis generation is transformed into hypothesis confirmation or refuting, as in this trial. Given the controversy surrounding nitrous oxide and clinical outcomes coupled with the availability of other fast-acting anesthetic agents, should this trial change management and result in an increase in the use of nitrous oxide? A recent study suggests that nitrous oxide is still relevant in clinical anesthesia and should be considered for certain patients, but how that fact and the current trial translates into local practice is up to the individual practitioner.[9]

Competing Interests

The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

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